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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/701,236
Filing Date: November 04, 2003
Appellant(s): CROOKE, STANLEY T.

John A. Harrelson, Jr.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 4, 2012 appealing from the Office action mailed March 16, 2011.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Application No. 10/701,264

Application No. 11/054,848

Application No. 10/701,007

Application No. 10/860,265

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

1, 71-73 and 76-79.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Wyatt et al. Nucleic Acids Research 1989, vol. 17, pages 7833-7842

5,801,154	Baracchini	9-1998

Monia et al. Journal of Biological Chemistry 1993, vol. 268, pages 14514-14522

Manche et al. Molecular and Cellular Biology 1992, vol. 12, pages 5238-5248

Inoue et al. Nucleic Acids Research 1987, vol. 15, pages 6131-6148

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 71-73 and 76-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Monia et al. (Journal of Biological Chemistry 1993, vol. 268, pages 14514-14522), Manche et al. (Molecular and Cellular Biology 1992, of record) and Baracchini et al. (US 5,801,154, of record).

The claims are directed to compositions comprising a duplex comprising 17 to 25 linked nucleotides in length wherein at least one strand comprises a plurality of 2'-hydroxyl pentofuranosyl sugars. In specific embodiments the strands of the duplex comprise gapmers and further comprise a 2'-sugar or phosphorothioate linkages. While not specifically recited, as set forth in the earliest priority document that provides written description support for the claimed subject matter (US 6,107,094, example 27a) these duplexes are artificial substrates for RNase enzymes that are useful for testing activity of such enzymes.

At the time the invention was made, those in the art routinely synthesized short duplexes containing ribonucleotide residues for the purpose of studying the activity and structural requirements of different enzymes. This is demonstrated by the teachings of Wyatt et al., Monia et al. and Manche et al.

Wyatt et al. teach that sensitivity of DNA and RNA to nucleases depends upon both chemical and conformational differences. For example, the 2'-OH makes ribonucleotides susceptible to alkaline hydrolysis and cleavage by ribonucleases, a

mechanism not available for cleavage of deoxynucleotides. Wyatt et al. further teach that RNase V1 from cobra venom is a widely used probe for double-stranded RNA that does not have a specific requirement for 2'-OH and is thus postulated to be like RNase H, which cleaves RNA-DNA duplexes. In order to probe the structural requirements of RNase V1 and RNase H, Wyatt et al. synthesized a series of 14 nucleotide duplexes wherein 2'-deoxyribonucleotides were site-specifically incorporated to allow study of duplexes containing covalently linked deoxy and ribo-nucleotides. These duplexes contain a sequence complementary to the ADCK2 gene (GenBank accession number NM_052853.3).

Monia et al. teach that susceptibility of unmodified phosphodiester oligonucleotides to nucleolytic degradation has made them unattractive molecules for oligonucleotide therapeutics. Chemical modifications have been introduced into oligonucleotides to increase their resistance to nucleolytic degradation, but these modifications can also possess additional properties that limit their usefulness, such as weaker affinity for RNA targets. Monia et al. performed a systematic study in which chimeric oligonucleotides containing various 2' sugar modifications were characterized for hybridization affinity and ability to direct target RNA cleavage by mammalian RNase H in order to study how to take advantage of the beneficial properties of oligonucleotide modifications while maintaining enzymatic substrate requirements. Monia et al. synthesized a 17-mer phosphorothioate having complementarity to Ha-ras for structure-function analysis of 2'-sugar modifications. These oligonucleotides were analyzed for hybridization affinity to a 25 nucleotide complementary RNA (see figure 2) and these

short duplexes were additionally analyzed for their ability to activate RNase H *in vitro* using HeLa cell extracts (see pages 14516-17 and materials and methods "RNase H analysis").

Manche et al. teach that the protein kinase DAI, the double-stranded RNA-activated inhibitor of translation, is a pivotal cellular regulatory enzyme that is an important element in the host antiviral response. Despite its importance as a regulatory enzyme, the interactions between DAI and its RNA effectors were complicated and incompletely understood. To better understand these interactions Manche et al. analyzed interaction of the enzyme with RNA duplex molecules of specified sizes ranging from 15-104 nt (see figure 1) in order to study binding and protection of dsRNA as well as activation and inhibition of the kinase.

At the time the instant application was filed those of ordinary skill in the art were familiar with the drawbacks of using nucleic acids in cellular environments or under conditions simulating such environments (particularly nucleolytic degradation as noted by Monia et al.) and were also familiar with antisense oligonucleotides used for research purposes.

Baracchini et al. provide additional teachings of the state of the art regarding use of modified nucleotides. Baracchini et al. teach that preferred oligonucleotides for use in cellular environments are modified in their sugar, backbone linkage and nucleobase composition and that such modifications have desirable properties such as enhanced target affinity and increased stability in the presence of nucleases. One particular type of modified oligonucleotide described at column 8 is chimeric oligonucleotides, including

gapmers. Baracchini et al. further teach that common sugar substituents include morpholino or peptide nucleic acid and further teach the use of phosphorothioate linkages.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make short duplex compounds that contain RNA residues and 2'-Omethyl modified nucleotides. Based on the teachings of Wyatt et al., Monia et al. and Manche et al., the person of ordinary skill would have reason to make short duplex oligonucleotides containing RNA residues and modified nucleotides for the purpose of studying enzyme structure and activity and would recognize that these duplexes could be made of various lengths, depending on the requirements of the particular enzyme being studied, for example, Monia et al. provide an explicit teaching of an artificial enzyme substrate comprising 17 and 25 nucleotide strands. Based on the teachings of Monia et al. and Baracchini et al, the person of ordinary skill in the art would have reason to incorporate 2'-sugar groups into the duplex because these references teach that nucleolytic degradation is a problem for nucleic acids and that stabilization of a duplex with modified nucleotides provide resistance to nucleases. Based on the knowledge available to the person of ordinary skill of the ways to incorporate modified nucleotides (including gapmer structures) and the usefulness of modified nucleotides in providing nuclease stability and binding affinity that is provided by the teachings of Monia et al, and Baracchini et al., the person of ordinary skill would be motivated to use these known modifications and modification patterns as a starting point for optimizing the stability and affinity of short duplexes. The person of ordinary skill in the art would

be able to predictably make duplex sequences comprising the claimed modifications at any desired position because these modifications and methods of nucleic acid synthesis are well known and routinely used by those in the art.

Thus, the invention of claims 1, 71-73 and 76-79 would have been obvious, as a whole, at the time the invention was made.

(10) Response to Argument

Appellants argue the Examiner has ignored the Declaration of David Corey with regard to the Manche and Barachinni references.

This is incorrect and the points in the declaration were addressed in the Final Office action. Dr. Corey's statements about the Manche reference are directed to two points: that Manche does not provide a reason to make duplexes comprising oligonucleotides 15 to 25 nucleosides in length because duplexes of that length failed to activate DAI and that Manche offers no reason to make chemically modified oligonucleotides because the duplexes used were synthesized enzymatically.

These arguments are not persuasive because Manche actually makes duplexes of oligonucleotides of 15-25 nucleotides in length; whether such compounds were able to activate DAI is not at issue in this application; the claims are not directed to compounds having any particular activity. While it is correct the compounds of Manche were enzymatically synthesized, the reason to make chemically modified oligonucleotides comes from the knowledge in the art that stabilization of oligonucleotides is desirable. This knowledge is demonstrated by the teachings of

Baracchini et al. and attested to by Dr. Corey in his remarks (see paragraph 12) regarding the relative instability and nuclease susceptibility of RNA.

Appellants are that Dr. Corey's declaration provides strong evidence that the pending obviousness rejection is based on impermissible hindsight instead of the teachings of the references themselves.

With regard to appellants' conclusion that the rejection is based on hindsight, as noted in MPEP 2145, any obviousness rejection is in a sense necessarily a reconstruction based on hindsight reasoning and is not improper if it takes into account only knowledge within the level of ordinary skill in the art at the time the claimed invention was made.

Based on the teachings of the cited reference the person of ordinary skill in the art would recognize that short duplexes were routinely used for the purpose of studying the activity and structural requirements of different enzymes, that these duplexes could be and were used under conditions where they might be susceptible to nuclease cleavage, and that one way to reduce this susceptibility was to include modified nucleotides such as 2'-OCH3. Moreover, the reason to make chemically modified oligonucleotides comes from the knowledge in the art that stabilization of oligonucleotides is desirable and not from the claimed oligonucleotide which has no activity or function associated with said molecule. As stated previously, this knowledge is demonstrated by the teachings of Baracchini et al. and attested to by Dr. Corey in his remarks (see paragraph 12) regarding the relative instability and nuclease susceptibility of RNA.

Appellants argue the references considered individually or as a whole do not suggest the claimed subject matter and argue the Wyatt reference describes duplexes used in *in vitro* experiments that did not contain nucleases other than the RNase V1 that was being studied, that the Monia article describes 17-mer oligonucleotides having a central gap region of 2'-deoxynucleotides and having 5' and 3' wing regions of 2'-OCH3 substituted nucleotides, and that the RNA duplexes of the Manche article were not chemically modified and state that none of these references provide teaching or suggestion to incorporate at least one 2'-OCH3 substituent group into both strands.

These arguments are not persuasive because none of these references was relied upon for an explicit teaching of a duplex modified in both strands. As stated in the rejection, these references are relied on to demonstrate that synthesis of short duplexes of RNAs for the purpose of studying the activity and structural requirements of different enzymes.

Appellants argue the experiments described in the Monia article utilized duplexes in which only one strand contained chemical modifications, and there would have been no reason to utilize substrates having chemical modifications in both strands in such experiments. The appellants argue that in the cited references only *in vitro* experiments are performed in order to conclude that modification of both strands is unnecessary. This reference was cited to demonstrate the fact that those in the field routinely performed experiments that mimicked intracellular conditions.

With regard to the Manche reference, appellants additionally argue the declaration of Dr. Corey points out that nothing about the nature or aim of the experiments described provides any reason to produce the claimed duplexes.

As stated previously, these arguments are not persuasive because Manche actually makes duplexes of oligonucleotides of 15-25 nucleotides in length; whether such compounds were able to activate DAI is not at issue in this application; the claims are not directed to compounds having any particular activity. While it is correct the compounds of Manche were enzymatically synthesized, the reason to make chemically modified oligonucleotides comes from the knowledge in the art that stabilization of oligonucleotides is desirable.

Appellants argue the Baracchini patent describes single-stranded antisense deoxynucleotides and does not suggest any reason to introduce chemical modifications into duplexes of oligomeric compounds.

It is correct that Baracchini does not teach double stranded compounds and does not exemplify compounds comprised of RNA, but this reference is not relied upon for such teachings, which are found in the Wyatt, Monia and Manche references. Baracchini is relied upon, along with Inoue, to provide teachings of the state of the art regarding use of modified nucleotides and to teach that specifically claimed modifications and motifs were known in the art.

Appellants argue there is no reason to incorporate chemical modifications into the strands of an oligomeric compound duplex at the time of the invention because the experiments described in the cited references do not involve conditions in which

undesired nucleolytic degradation of such duplexes could have occurred. Appellants argue that for *in vitro* experiments only endonucleases being studied were present in the reaction mixtures and no other enzymes were present.

This argument is not persuasive because the *in vitro* experiments described in the references are not the only type of experiments that could be performed. While the references might have used only a single enzyme, those in the art were nevertheless aware that experiments could be done under conditions that mimic *in vivo* conditions where modification would be considered desirable.

Appellants further argue the experiments in which nucleic acids were introduced into cells or were treated with cellular extracts, single-stranded oligonucleotides targeted against full-length mRNAs were used in such experiments, and double- stranded duplexes were not utilized. None of the references therefore describes experiments in which double-stranded nucleic acids were introduced into an environment in which undesired nucleolytic degradation of the duplexes could have occurred.

This is not correct. As noted in the rejection Monia does use short duplex RNAs in cell extract experiments. Monia states at page 14517, column 2 that the ability to direct RNase H cleavage of a complementary RNA by 2'-O-methyl deoxy gap oligonucleotides was determined *in vitro* using HeLa nuclear extracts and refers to figure 4. The legend for figure 4 states, "a synthetic, end-labeled, 25-mer RNA containing mutant Ha-ras codon 12 sequences…was preannealed with the appropriate oligonucleotide and treated with HeLa RNase H for 10 min at 37 °C. Following termination of reactions, cleavage products were resolved on a 20% acrylamide gel

under denaturing conditions. A, 2 μg of HeLa extract added; B, 0.2 μg of HeLa extract added."

Appellants argue the claimed compounds would not have been obvious to those skilled in the art at the time of the invention because the cited references describe successful experiments performed to characterize particular enzymes and no reason has been provided why one would have been motivated to repeat those experiments with more stable substrates.

This is not persuasive because the rejection is not predicated on the idea that those in the field would only repeat experiments and no new experiments would ever be performed. Wyatt, Monia and Manche demonstrate that artificial nuclease substrates are useful for studying enzymes; based on these teachings one of ordinary skill would recognize that similar substrates could be used for either further experiments of these enzymes under cellular or in vivo conditions or could be used to study other, new enzymes.

Based on the teachings of the cited reference the person of ordinary skill in the art would recognize that short duplexes were routinely used for the purpose of studying the activity and structural requirements of different enzymes, that these duplexes could be and were used under conditions where they might be susceptible to nuclease cleavage, and that one way to reduce this susceptibility was to include modified nucleotides such as a sugar surrogate. Therefore the claimed invention would have been obvious to the person of ordinary skill in the art at the time the invention was made.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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